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Original Article

Pan-Driver-Negatives *versus* Epidermal Growth Factor Receptor Mutants for C-Stage IA Lung Adenocarcinoma with Ground-Glass Opacity

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Purpose: We aimed to verify the prognosis of epidermal growth factor receptor (EGFR) mutation of clinical (c)-stage IA lung adenocarcinoma with the ground-glass opacity (GGO) component.

Methods: We evaluated 226 cases of surgically resected c-stage IA lung adenocarcinoma with GGO component. Endpoints were overall survival (OS) and recurrence-free survival (RFS). Kaplan–Meier analysis and the log-rank test were used to estimate the survival differences. Prognostic factors were assessed using the univariable and multivariable Cox proportional hazards model.

Results: Among the 226 cases, 177 cases harbored the EGFR-mutant adenocarcinoma with the GGO component. The mean duration of follow-up time was 54.4 ± 1.2 months. The 5-year OS and RFS did not differ significantly between the EGFR-mutant and wild-type groups (5-year OS 100% vs. 94.3%, hazard ratio [HR] 0.276, $P = 0.168$; 5-year RFS 94.7% vs. 95.7%, HR 0.873, $P = 0.864$). Multivariable Cox hazard model revealed that radiologically solid component size ($P = 0.010$) and pathological node-positive ($P = 0.036$) were significant predictors of an inferior RFS.

Conclusion: EGFR-mutant was not a prognostic factor of OS and RFS for c-stage IA lung adenocarcinoma with the GGO component. Radiologically solid component size and pathological lymph node status were independent prognostic factors of worse RFS.

Keywords: epidermal growth factor receptor, prognosis, lung adenocarcinoma, ground-glass opacity

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Introduction

Epidermal growth factor receptor (EGFR) has been suggested to be a signature event and critical for the initiation of non-small cell lung cancer (NSCLC), which is thought to be involved in the development of tumor malignancy and correlated with the poor prognosis.[1,2] To date, targeted therapeutic strategies of EGFR tyrosine kinase inhibitors (EGFR-TKIs) remain the standard first-line treatment for patients with EGFR mutations.[3] Thus, for patients with advanced NSCLC, harboring EGFR sensitizing mutations can be a signature of superior treatment landscape and prognosis compared to the patients with EGFR wild type. However, the effect of

EGFR mutation on the prognosis of primary lung cancer after curative surgery remains controversial. Several studies have indicated that EGFR mutation is a favorable prognostic factor for patients with pathologic (p)-stage IB to IIIA, while had no effect on the prognosis of stage IA NSCLC.[4,5] In contrast, it was reported that EGFR mutation was correlated with an increased risk of recurrence in the clinical (c)-stage T1c/T2a radiologically lung adenocarcinoma with radiologically pure-solid.[6] Although early stage lung adenocarcinoma has not been published, different prognosis and biological heterogeneity have been suggested in our prior study. A better prognosis and a higher proportion of EGFR mutation have been reported in lung adenocarcinoma with ground-glass opacity (GGO) component, particularly in female patients with adenocarcinomas who had never smoked. In the progression schema of early stage lung adenocarcinoma, EGFR mutations have been considered involved in the early phase of lung adenocarcinoma development and established as a key driver of tumor cell progression.[7] In brief, the prognostic role of EGFR mutation in the adenocarcinoma with GGO component has not been well defined. In this study, we proposed to explore the prognosis of c-stage IA lung adenocarcinomas with GGO components harboring EGFR mutation status and wild type. We hypothesized that adenocarcinomas with GGO components have favorable long-term outcomes, even though harboring activation EGFR mutations.

Patients and Methods

Study population

Between 2013 and 2016, we retrospectively evaluated 484 patients with complete surgically resected (R0 resection) c-stage IA lung adenocarcinoma with GGO components as primary tumors. All patients underwent standard systematic sampling or systematic lymph node dissections in intraoperatively staging the mediastinum. Further, patients harboring other gene mutant (without EGFR-mutant) or not receiving genetic testing were excluded. Thus, only EGFR-mutant and wild patients were included to eliminate the influence of other driver mutations. Then, 226 patients, including 177 EGFR-mutant and 49 wild cases, were included in the final analyses. The patients' information and follow-up data were reviewed independently by Ming Li, Junjie Xi, Huan Zhang, and Fenghao Sun. The staging was reclassified according to the eighth edition of the tumor node metastasis (TNM) classification.[8] This retrospective review was performed under a waiver of authorization approved by the institutional review board of Zhongshan Hospital, Fudan University (B2018-137R).

Radiologic evaluations

For all patients, the data from preoperative thin-section computed tomography (CT) scans were reviewed independently by Ming Li, Junjie Xi, and Qun Wang. Solid component size and GGO component were determined preoperatively based on a thin-section CT scan with a 1-mm collimator. The lung was photographed with a window level of −500 to −700 Hounsfield units (HU) and a window depth of 1000–2000 HU, which was labeled as the "lung window," and a window level of 30–60 HU and window depth of 350–600 HU, which was labeled as the "mediastinal window." The consolidation/tumor ratio (CTR) was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-section CT to reflect the tumor aggressiveness.[9] Positron emission tomography (PET) for managing patients with c-stage I tumors with GGO component is not recommended at our hospital. It is not widely available in our country for economic reasons.[10] Similarly, preoperative mediastinal lymph node staging, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, is not recommended for patients with clinical I adenocarcinomas at our hospital.[11]

EGFR-mutant evaluations

The final pathology results were confirmed from surgical specimens and paraffin section diagnosis. Molecular pathological testing for aberrations in patients with lung adenocarcinoma in our hospital was provided as a panel of EGFR, Kirsten-Ras, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform, and human epidermal growth factor receptor-2. Fluorescence in situ hybridization was used as the detection method for anaplastic lymphoma kinase-positive, receptor tyrosine kinase proto-oncogene tyrosine-protein kinase-1 (ROS-1)-positive, and rearranged during transfection (RET)-positive lung adenocarcinoma. The amplification refractory mutation system-polymerase chain reaction (PCR) and next-generation sequencing technology were used for EGFR gene mutation testing at our hospital.[12]

Statistical analysis

Descriptive statistics were used to summarize the baseline of the study population. Characteristics are presented as means (standard deviation) or median

(interquartile range) for continuous variables and absolute counts (percentages) for categorical variables. An unpaired t-test or chi-square test was used to compare each categorical variable. For the prognostic evaluation, the primary endpoints were overall survival (OS) and recurrence-free survival (RFS). OS and RFS were estimated by the Kaplan–Meier method.[13] The log-rank test performed the between-group comparison of survival. Univariate and multivariate analyses, including all covariates, were performed using the Cox proportional hazards model to adjust confounding variables for OS and RFS.[14] All *P* values were two-sided. All statistical analyses were performed with R 4.0.3 software (© 2016 The R Foundation, Vienna, Austria).

Data availability statement

The data underlying this article cannot be shared publicly due to ethical/privacy reasons. The data will be shared at reasonable request to the corresponding author.

Results

Clinicopathological characteristics of patients

The mean duration of follow-up time was 54.4 ± 1.2 months, with a median duration of 52.6 ± 1.5 months. The study cohort's baseline characteristics and follow-up information are summarized in **Table 1**. A total of 177 EGFR-mutant and 49 wild-type patients diagnosed as c-stage IA lung adenocarcinoma with GGO components were included (flow diagram, **Fig. 1**). In all, 13 patients were classified into p-stage IB postoperatively. Only with regard to sex, there was a statistically significant difference in sex distribution between the EGFR-mutant and wild-type groups ($P = 0.021$). Female patients made up a greater proportion of patients harboring EGFR mutation. Both groups were not different in their other baseline characteristics.

Survival outcomes between EGFR-mutant and wild groups

Regarding the postoperative events in 226 patients, only 4 cases died, and ten patients had recurrence (2 patients in the wild-type group and 8 patients in the EGFR-mutant group) during the observation period. Five of the relapsed patients received adjuvant treatments, including targeted therapy, chemotherapy, and sequential chemotherapy and radiation. Distant relapse was the most common first site of recurrence, including bone metastases (n = 2), liver metastases (n = 1), and contralateral lung metastases (n = 2). The remaining five patients were not diagnosed and treated at our hospital, and the specific sites of disease recurrences were not clear.

The 5-year OS and RFS of all cohort were 98.9% and 95.0%, respectively. When comparing outcomes between the EGFR-mutant group and wild-type group, the differences of 5-year OS and RFS were not significant (5-year OS 100% vs. 94.3%, hazard ratio [HR] 0.276, $P = 0.168$, 95% confidence interval [CI] 0.026–2.984; 5-year RFS 94.7% vs. 95.7%, HR 0.873, $P = 0.864$, 95% CI 0.197–3.876; **Figs. 2A** and **2D**). Next, we stratified the cohort according to p-stage for further analysis of cases with p-stage IA or IB but c-stage IA. Similarly, no difference was appreciated in OS and RFS between the EGFR-mutant and wild-type groups both for p-stage IA (5-year OS 100% vs. 94.1%, HR 0.202, $P = 0.184$, 95% CI 0.019–2.136; 5-year RFS 96.3% vs. 95.6%, HR 0.569, $P = 0.508$, 95% CI 0.083–3.907; **Figs. 2B** and **2E**) and IB (3-year OS 100% vs. 100%, $P > 0.999$; 3-year RFS 72.7% vs. 100%, $P = 0.437$; **Figs. 2C** and **2F**) cases.

Survival outcomes between EGFR-mutant and wild groups stratified by CTR

CTR is considered an important prognostic factor in early stage lung adenocarcinoma with GGO components, which reflects the radiological invasion of tumor.[15] In this study, cases were divided into three groups based on the proportion of GGO according to the CTR to represent the different invasion ability: A, CTR ≤ 0.5; B, $0.5 < \text{CTR} \leq 0.75$; and C, $0.75 < \text{CTR} \leq 1.0$. Comparison revealed no difference in OS and RFS between the EGFR-mutant and wild-type groups for every CTR: CTR ≤ 0.5 (5-year OS 100% vs. 100%, $P > 0.999$; 5-year RFS 100% vs. 100%, $P > 0.999$; **Figs. 3A** and **3D**), $0.5 < \text{CTR} \leq 0.75$ (5-year OS 100% vs. 92.3%, HR 0.188, $P = 0.185$, 95% CI 0.004–8.384; 5-year RFS 91.6% vs. 93.8%, HR 1.112, $P = 0.923$, 95% CI 0.140–8.848; **Figs. 3B** and **3E**), and $0.75 < \text{CTR} \leq 1.0$ (5-year OS 100% vs. 83.3%, HR 0.481, $P = 0.596$, 95% CI 0.025–9.274; 5-year RFS 84.6% vs. 83.3%, HR 0.784, $P = 0.832$, 95% CI 0.092–6.678; **Figs. 3C** and **3F**).

Univariate and multivariate analyses in Cox proportional hazards model

Enter and forward stepwise procedures were used to determine the combination of prognostic factors for the survival outcomes in the Cox proportional hazards model. However, EGFR mutation was not an

Table 1 Clinicopathological characteristics of pathologic stage I lung adenocarcinoma with GGOs between EGFR-mutant and wild groups

Characteristics	EGFR mutant	Wild type	*P* value
Total evaluated	177	49	
Age, y, median (IQR)	61 (54, 68)	60 (56, 67)	0.996
Sex, n (%)			0.021
Female	125 (70.6)	26 (53.1)	
Male	52 (29.4)	23 (46.9)	
Smoking history, n (%)	14 (7.9)	3 (6.1)	0.475
Solid component size, mm, median (IQR)	8 (5,12)	9 (5.25,12)	0.855
CTR, median (IQR)	0.53 (0.33,0.64)	0.50 (0.37,0.65)	0.499
WHO classification, n (%)			0.317
AIS	3 (1.7)	0 (0)	
MIA	29 (16.4)	11 (22.4)	
Invasive adenocarcinoma	114 (64.4)	32 (65.3)	
Variants and undetermined	31 (17.5)	6 (12.2)	
*Predominant subtype			0.317
AIS	3 (1.7)	0 (0)	
MIA	29 (16.4)	2 (4.1)	
Lepidic predominant	18 (10.2)	7 (14.3)	
Acinar predominant	92 (52.0)	23 (46.9)	
Papillary predominant	4 (2.3)	2 (4.1)	
Two or more predominant	30 (16.9)	6 (12.2)	
*Undetermined	1 (0.6)	0 (0)	
c-stage T classification, n (%)			0.668
c-stage T1mi	53 (29.9)	12 (24.5)	
c-stage T1a	66 (37.3)	22 (44.9)	
c-stage T1b	50 (28.2)	14 (28.6)	
c-stage T1c	8 (4.5)	1 (2.0)	
p-stage T classification, n (%)			0.635
p-stage T1mi	5 (2.8)	1 (2.0)	
p-stage T1a	66 (37.3)	23 (46.9)	
p-stage T1b	79 (44.6)	17 (34.7)	
p-stage T1c	16 (9.0)	6 (12.2)	
p-stage T2a	11 (6.2)	2 (4.1)	
Pathological pleural invasion, n (%)	8 (4.5)	2 (4.1)	0.895
EGFR gene aberration, n (%)			–
Exon 18	1 (0.6)	–	
Exon 19	75 (42.4)	–	
Exon 21	101 (57.1)	–	
Operative procedure, n (%)			0.439
Lobectomy	110 (62.1)	30 (61.2)	
Segmentectomy	36 (20.3)	7 (14.3)	
Wedge resection	31 (17.5)	12 (24.5)	
Relapsed cases, n (%)	8 (4.5)	2 (4.1)	0.895

Values are number (%) or median (IQR).

**P* value determined by the unpaired *t* test or chi-square test. *Undetermined refers to the pathological types that are still difficult to classify after reanalysis by pathologists or the loss of pathological information (very few). *IASLC/ATS/ERS classification: The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification.

CTR: consolidation/tumour ratio; WHO classification: World Health Organization classification; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; EGFR: epidermal growth factor receptor; IQR: interquartile range; GGO: ground-glass opacity

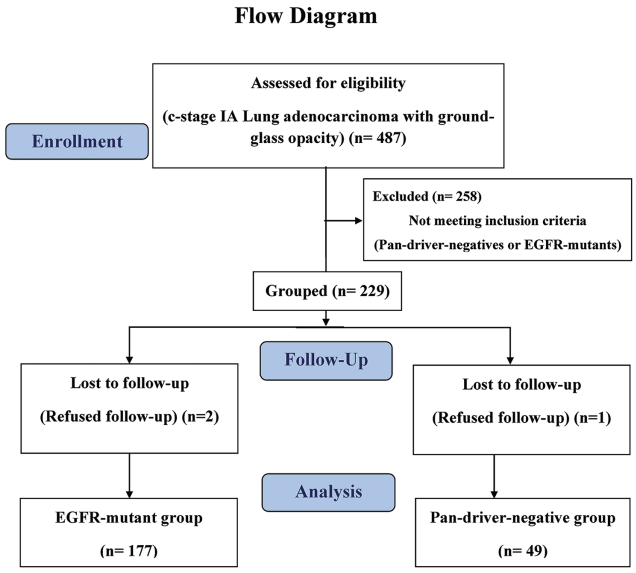

Fig. 1 Flow diagram for patient inclusion, comparison groups, and follow-up.

independent significant clinical predictor of superior OS and RFS in the entire cohort in the multivariable Cox proportional hazard model (**Table 2**). Multivariate analysis showed that there were no independent prognostic factors for OS. Thus, multivariate Cox regression for OS was not performed further. Moreover, it was demonstrated that radiologically solid component size (P = 0.010) and pathological node-positive (P = 0.036) were significant clinical predictors of worse RFS.

Discussion

Many studies have indicated that lung adenocarcinoma with the GGO component has a superior prognosis and different population characteristics compared to solid lung adenocarcinoma.[16–19] Similar results were also observed in our previous studies, which suggested that adenocarcinomas with GGO components may have

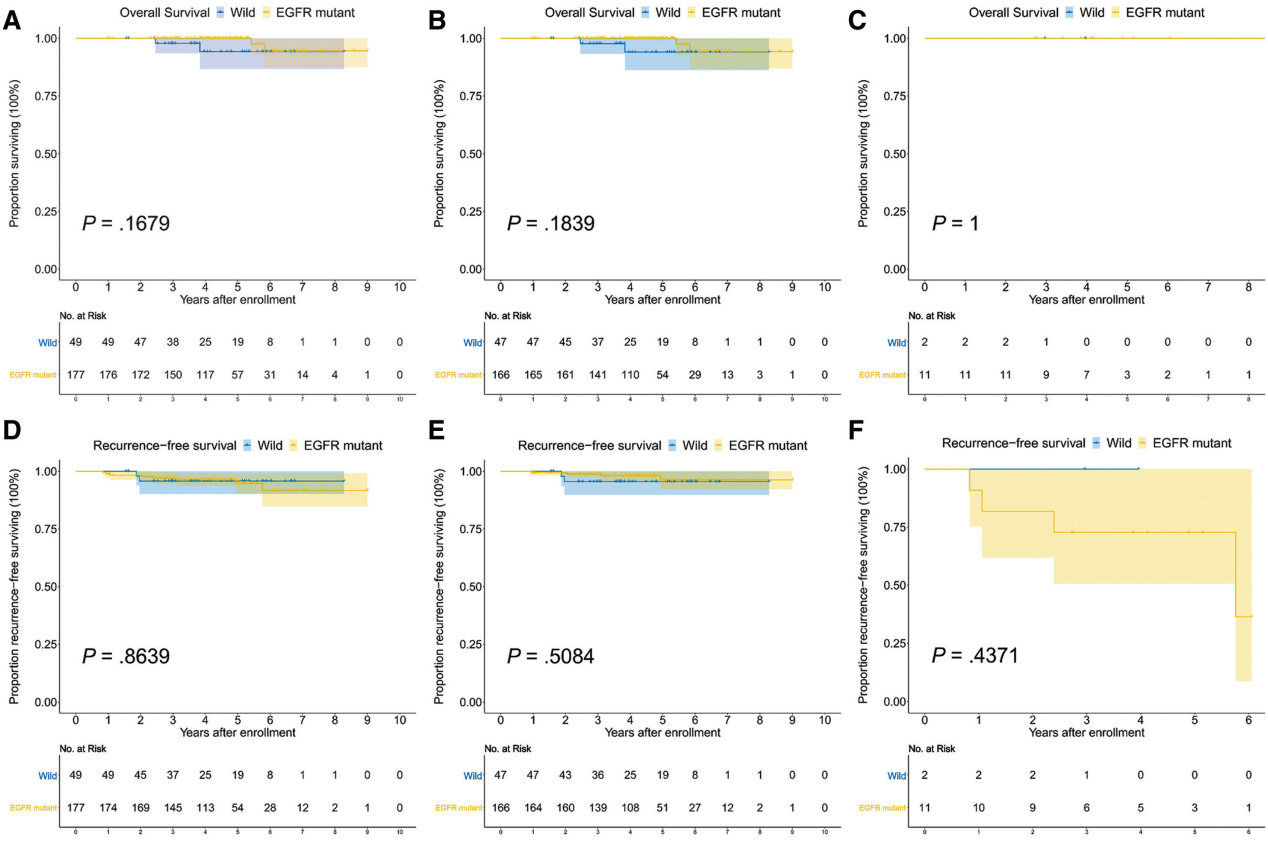

Fig. 2 Survival outcome between EGFR-mutant and wild groups in c-stage IA lung adenocarcinoma with the GGO component (overall: **A**, OS; **D**, RFS; p-stage IA: **B**, OS; **E**, RFS; p-stage IB: **C**, OS; **F**, RFS). The 5-year OS and RFS were not significantly different between the 2 groups. OS: overall survival; RFS: recurrence-free survival; GGO: ground-glass opacity; EGFR: epidermal growth factor receptor; c: clinical

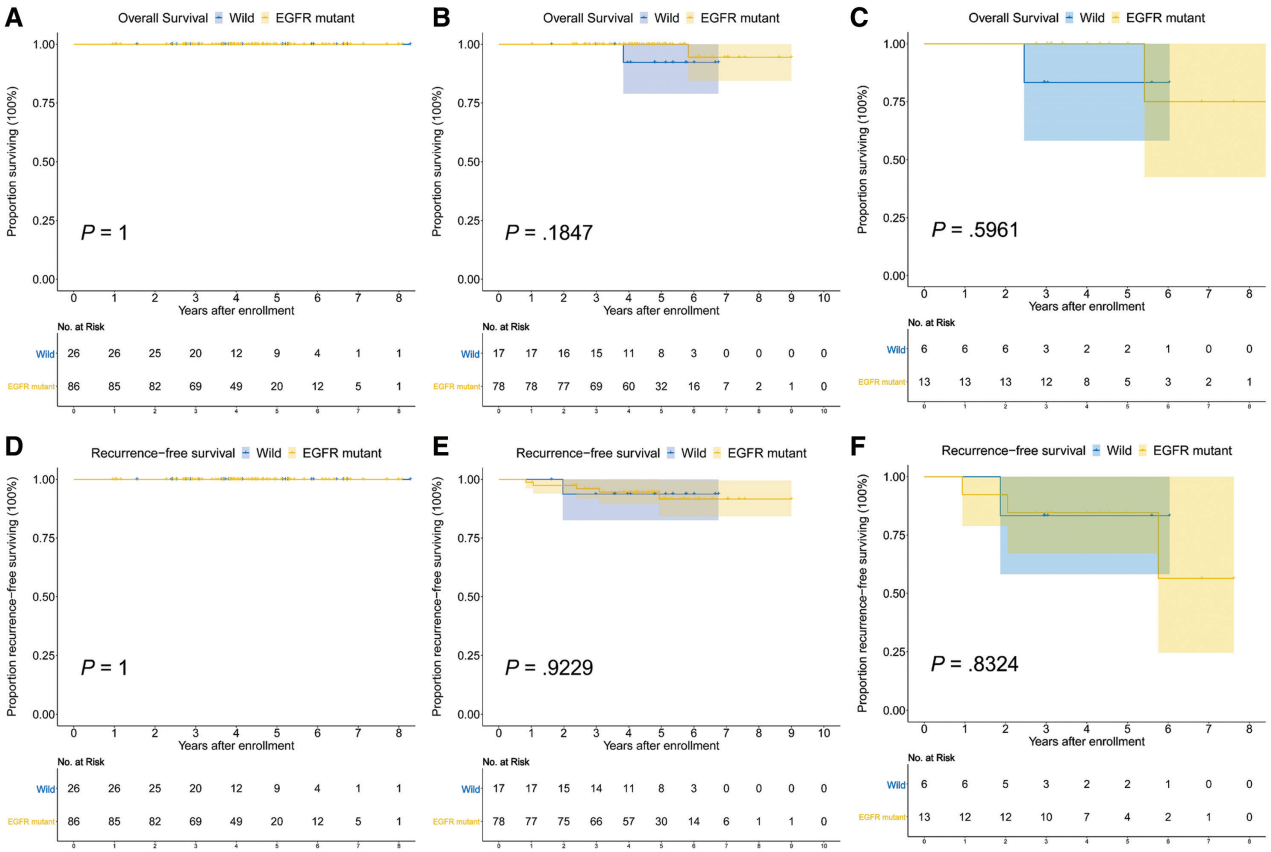

Fig. 3 Survival outcome of EGFR-mutant and wild groups regarding OS in CTR ≤0.5 (**A**), 0.5 <CTR ≤0.75 (**B**), and 0.75 <CTR ≤1.0 (**C**); and survival outcome regarding RFS in CTR ≤0.5 (**D**), 0.5 <CTR ≤0.75 (**E**), and 0.75 <CTR ≤1.0 (**F**) between the nearly pure-solid and pure-solid groups. OS: overall survival; RFS: recurrence-free survival; CTR: consolidation/tumor ratio

inter-tumor heterogeneity and different biologic properties. GGO-predominant adenocarcinomas differed from the pure-solid adenocarcinomas, which was more prone to be diagnosed in female patients who had never smoked. It was also reported that patients with GGO-predominant adenocarcinomas might have a higher proportion of EGFR mutations, which may be explained by a nonlinear progression of the pure-solid adenocarcinomas.[7] Although the prognostic impact of EGFR mutation in non-small-cell lung cancer patients has been reported in the previous literature, the prognostic role of EGFR mutations was conflicting.[20] Generally, it is considered that EGFR mutations may be closely associated with accelerated tumor growth, but not tumor invasiveness. For pure-solid lung adenocarcinoma, the presence of an EGFR mutation may be associated with an inferior RFS, which also remains controversial.[20] Thus, we aimed to evaluate the prognostic role of the EGFR mutation on adenocarcinomas with GGO components in the Chinese patients' cohort.

We included 226 patients, including 177 EGFR-mutant cases, in our study cohort. Similarly, among the 226 cases, a higher percentage of female patients had never smoked (62.8%). However, it is still unclear why these female patients who had never smoked were more likely to suffer from GGO-predominant adenocarcinomas. Interestingly, in our daily clinical practice, we found that similar to maternally inherited, if a woman had GGO-predominant adenocarcinoma, her mother or daughter would also screen positive for ground-glass lesions. However, the lack of epidemiologically confirmed data precludes such an interesting conclusion. As we are showing, we did not observe any significant differences in OS and RFS between the EGFR-mutant and wild-type groups, even for p-stage IB patients. EGFR mutation was not an independent prognostic factor both for OS and RFS in the multivariable Cox proportional hazard model.

The presence of the GGO component often indicates an excellent outcome for the patient. Patients with

Table 2 Univariable and multivariable analyses for OS and RFS

Variables	OS			
	Univariable HR (95% CI)	*P value	Multivariable HR (95% CI)	*P value
Age (yrs)	1.043 (0.933–1.165)	0.459	–	–
Gender (male)	1.551 (0.161–14.912)	0.704	–	–
Smoking	22.928 (0.000–>10^3)	0.695	–	–
Solid component size (mm)	0.980 (0.815–1.179)	0.831	–	–
WHO classification (invasive)	26.195 (0.000–>10^3)	0.590	–	–
Pathological pleural invasion (PL+)	21.235 (0.000–>10^3)	0.810	–	–
Pathological lymph node (pN+)	20.631 (0.000–>10^3)	0.872	–	–
Operative procedure (lobectomy)	0.434 (0.064–3.264)	0.456	–	–
EGFR-mutation	0.275 (0.039–1.961)	0.198	–	–
	RFS			
Age (yrs)	1.029 (0.964–1.098)	0.389		
Gender (male)	1.208 (0.312–4.676)	0.784		
Smoking	1.363 (0.172–10.766)	0.769		
Solid component size (mm)	1.123 (1.032–1.223)	0.007	1.122 (1.028–1.226)	0.010
WHO classification (invasive)	27.421 (0.025–>10^3)	0.354		
Pathological pleural invasion (PL+)	12.426 (3.170–48.716)	<0.001	4.485 (0.933–25.145)	0.060
Pathological node (pN+)	25.278 (5.2237–122.01)	<0.001	8.014 (1.150–55.848)	0.036
Operative procedure (lobectomy)	0.831 (0.234–2.957)	0.775		
EGFR-mutation	1.145 (0.243–5.399)	0.864		

*P value in the Cox proportional hazards model.
OS: overall survival; RFS: recurrence-free survival; HR: hazard ratio; CI: confidence interval; WHO: World Health Organization; EGFR: epidermal growth factor receptor

EGFR-mutant adenocarcinomas often prompt poor RFS outcomes and better OS outcomes. However, the true prognostic significance of EGFR mutations could not be determined in OS because EGFR mutation status suggests that patients could benefit from EGFR-TKIs. Our results showed that patients with GGO-predominant adenocarcinomas had an excellent prognosis both in OS and RFS, with or without EGFR mutations, which indicated that these patients could obtain highly desirable outcomes after lobectomy or sublobectomy. The conventional wisdom held that pure-solid lung adenocarcinomas and GGO-predominant adenocarcinomas underwent different patterns of linear progression. Some of the pure-solid adenocarcinomas were expected to reflect a nonlinear progression that would deviate from de novo invasive adenocarcinomas.[21] In the linear progression of adenocarcinomas with GGO components, EGFR mutation was an important factor promoting tumor growth but did not correlate with tumor malignancy. Thus, for pure-solid adenocarcinomas, EGFR mutations seem to confer a poor prognosis of RFS. However, this facilitation may be affected by the presence of GGO components in the part-solid adenocarcinomas, which contributed to no significant outcomes between the two groups in this study. However, it remains unclear how the presence of the GGO component affects the prognosis. Our previous studies have contrasted the single-cell transcriptome atlas of lung adenocarcinoma featured with GGO.[22] We speculated that the difference might be related to the tumor microenvironment and immune cell infiltration change.

Stratified subgroup analysis according to the CTR also showed no outcome difference between the EGFR-mutant and wild-type groups, even for the solid-predominant (0.75 ≤CTR <1.0) group. It was considered that CTR could predict pathological invasiveness in peripheral clinical IA lung cancer in the Japan Clinical Oncology Group 0201 (JCOG0201) trial. The JCOG0802/WJOG4607L, JCOG0804/WJOG4507L, and JCOG1211 trials performed a full comparison of outcomes among standard lobectomy, segmentectomy, and wedge resection.[23,24] Limited surgical resection, including anatomical partial lobectomy, for patients with GGO-dominant early-stage lung adenocarcinoma has

been widely accepted by many thoracic surgeons. However, our results demonstrated that radiologically solid component size (P = 0.010) and pathological node-positive (P = 0.036) were independent prognostic factors of worse RFS.

In this study cohort, two cases were diagnosed with p-stage N2 after the operation, with no lymph nodes involved in the preoperative CT scans. Both cases experienced relapse after surgery and harbored EGFR L858R mutations. Regrettably, the two cases were not performed by PET/CT scans for medical cost reasons. Thus, we suggested that clinical staging of every suspected lung cancer uses PET scan as conditions permit, even of the patients with GGO-dominant adenocarcinomas. This study also had some limitations that should be mentioned. First, this study was a retrospective study from a single institution. Second, PET/CT scanning was not performed in some patients. This missing information may restrict the validity of the analysis.

This study is limited by its retrospective nature and small sample size, making it a pilot study character. The propensity score matching method should be used to minimize the influence of other confounders, which we hope to address in a future large-sample study.

Conclusion

In conclusion, unlike the pure-solid lung adenocarcinoma, for c-stage IA radiologically adenocarcinoma with GGO component, EGFR mutation was not a prognostic factor of survival and recurrence. Radiologically solid component size and pathological lymph node status were prognostic factors of worse RFS. Lung adenocarcinoma with GGO component may be a distinct disease.

Author Contribution

Ming Li: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, and writing – review and editing; Junjie Xi: conceptualization, data curation, investigation, methodology, project administration, resources, supervision, and writing – review and editing; Huan Zhang: data curation, formal analysis, investigation, methodology, software, validation, visualization, and writing – review and editing; Xing Jin: data curation, formal analysis, investigation, methodology, software, validation, and visualization; Jianrong Zhang: biostatistical professional; Mingxiang Feng: conceptualization, funding acquisition, and writing – review and editing; Cheng Zhan: resources and writing – review and editing; and Qun Wang: funding acquisition, project administration, resources, and supervision.

Ethics Statement

This retrospective review was performed under a waiver of authorization approved by the institutional review board of Zhongshan Hospital, Fudan University (B2018-137R).

Availability of Data

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request (requiring the ethics committee's approval).

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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